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The problems of clinical trials and registries in rare diseases

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Summary
Clinical trials to evaluate patients affected by rare diseases are often hampered by the difficulty of recruiting a critical sample size. Registries for rare conditions are thus extremely powerful tools for overcoming recruitment problems. Here we present and discuss the international experience with alpha1-antitrypsin deficiency achieved by the Alpha One International Registry, and national experience obtained with a large series of patients with pulmonary alveolar proteinosis.

Introduction

The current definition of a rare disease is a medical condition occurring in <50, 000 individuals among the European general population. This implies that, for some of these conditions, a general practitioner or even a specialist may see only one or two cases during his/her professional career. It is therefore conceivable that isolated patients affected by a rare disorder managed by a single physician will not contribute to progress in the understanding of the epidemiology, pathophysiology, natural history and efficacy of treatments for such disorders. However, when isolated patients are included in large cohorts that are eventually submitted to careful analysis we can greatly improve our knowledge of these conditions.

Registries are powerful tools in improving our understanding of rare diseases. Taking advantage of our experience in two rare respiratory diseases: alpha1-antitrypsin deficiency (AATD) and pulmonary alveolar proteinosis (PAP), we describe how registries (or a large cohort of patients) can help physicians to better manage the disease and design clinical trials.

AATD: the Alpha One International Registry (AIR)

AATD is characterized by reduced blood levels of the serine protease inhibitor alpha1-antitrypsin, leading to an increased risk of developing pulmonary emphysema and chronic liver disease. AATD is probably the most common inherited rare

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disorder in Western countries.[1] Even though the disorder was identified for the first time in 1963, three decades later its relative infrequency (1 in 1600—2000) is still the major handicap to understanding and designing interventions.

In 1997 a World Health Organization meeting recommended the establishment of national and international registries to facilitate data collection and collaborative research, and to help create a patient resource bank for the design and conduct of suitably powered clinical trials.[2] To comply with these recommendations, the Alpha One International Registry (AIR) was initiated with the following four main objectives: 1) to establish an international database of patients, including their demographic details; 2) to promote basic and clinical research on AATD and to coordinate these activities; 3) to collect, assess and disseminate information concerning all aspects of AATD; and 4) to encourage the support and awareness of AATD.

Most of the aims of AIR have been now successfully accomplished. Stockley and co-workers recently described that by 2005 the registry included 21 countries from four continents.[3] A web-enabled questionnaire has been developed that may be completed online by authorized physicians. Data quality is audited by the central AIR database manager and a national delegate, who supervises all national entries. By the time Stockley's data was published in 2007, a total of 2627 AATD individuals were enrolled in AIR, which is the largest series of AATD individuals in the world. Currently, more than 4000 AATD are included.

Another accomplishment concerns the successful submission of proposals to the European Commission Framework Project. Two projects were approved and funded by the 5th Framework Project: the Software Performance and Reproducibility in Emphysema Assessment: Demonstration (SPREAD) project (QLG1-2000-0152) and the AIR genetics project (QLG2-2001-01021). The first represents a consortium of AIR investigators aiming to explore lung densitometry assessed by computed tomography (CT) as a possible outcome for longitudinal studies in pulmonary emphysema.[4] Of particular interest, the results obtained by the consortium have been subsequently utilized in an AATD clinical trial (see below).

The second project is very ambitious: to collect DNA samples from AIR members' PI*ZZ AATD siblings who currently smoke, yet have discordant lung function, to investigate the possible presence of genetic factor(s) other than the AAT gene that may increase the risk of developing emphysema or, alternatively, protect the lung from emphysema development. It is a very long and labour-intensive project: the cohort of siblings has been identified and DNA samples have been submitted to two runs of genome-wide linkage analysis. Several linkage peaks have been identified and, after fine mapping, candidate gene analysis is currently in progress.

Another project still in progress was funded by the EC under the call of Public Health — 2006. Patient Associations and Alpha1-antitrypsin Deficiency (PAAIR) is a project in which patient support groups and national AATD registries from the Netherlands, Germany and Italy work together to evaluate the impact of reference centres for AATD on morbidity and mortality, and the outcomes of an effective collaboration.

A major goal of AIR has been to design clinical trials and recruit AATD patients. In particular, two important trials have been completed with its help. One is the AATD branch of a trial aimed at evaluating the potential effectiveness of an agonist of the γ-retinoid receptor to prevent the progression of emphysema, using CT scan densitometry as a measure of efficacy. The trial in patients with AATD-associated emphysema preceded on common emphysema without AATD, and is currently in the final stage of data analysis. Another important trial, which expanded a previous report,[5] has been completed and recently published. The study demonstrated in 77 AATD patients recruited among the national registries of the UK, Denmark and Sweden, treated weekly with alpha1-antitrypsin infusions for 2 years, that computed tomography was more sensitive than other measures of emphysema progression, such as physiology and health status.[6] Because of its exploratory nature, the trial was not powered to demonstrate the efficacy of the replacement therapy; nevertheless, the densitometric analysis showed a trend suggestive of treatment benefit.

It is important to reiterate that without organizations like the AIR, clinical trials for rare diseases would practically never be conducted. Another relevant aspect is that emphysema associated with AATD has been used to pioneer the use of CT densitometry as an outcome in clinical trials. It is conceivable that the treatment of emphysema in common COPD will benefit from the experience gained in AATD studies.

Pulmonary alveolar proteinosis: not only rare but also neglected

Pulmonary alveolar proteinosis (PAP) is an extremely rare but ubiquitous syndrome (not a single disease) occurring at all ages and characterized by the accumulation of surfactant and surfactant by-products within the airspaces. A typical feature of PAP is the variable clinical history, ranging from spontaneous improvement or resolution, to progressive respiratory failure. Inspite of the exceptional progress achieved in the understanding of the pathophysiology of PAP during the last 15 years[7] it is still a neglected condition, even in Western countries. Some features of PAP and AATD in Europe are compared in Table 1.

The history of PAP is marked by two important milestones: the introduction of whole-lung lavage (WLL) to clinical practice, and the discovery that PAP arises because of disturbances in GM-CSF signalling. The first seminal discovery had a direct impact on the natural history of PAP: first characterized by a death rate of 30%, it was no longer considered potentially fatal after the introduction of WLL in the 1960s.[8] From this point of view, WLL revolutionized the course of PAP.

The discovery that GM-CSF played a crucial role in lung-surfactant homeostasis, and subsequently that PAP cases previously referred to as idiopathic or primary were actually autoimmune disorders associated with the presence in the blood and lung of autoantibodies neutralizing GM-CSF,[9] opened the way to the potential use of exogenous GM-CSF to treat PAP, especially in those cases refractory to WLL or that could not be treated by this invasive procedure.

An obvious difficulty in the design of a study to demonstrate GM-CSF efficacy in PAP is the lack of disease

Table 1 Comparative features of alpha1-antitrypsin deficiency (AATD) and pulmonary alveolar proteinosis (PAP) in Europe.

	AATD	PAP
Incidence (*n*/100 000)	25	0.1
Included in national lists for rare diseases	Yes	Some countries
National registries	Yes	No
International registry	Yes	No
Reference-centre network	Yes	No
Patient support groups	Yes	No
Therapy available (paid for by the national health service)	Some countries	No

registries, such as those available in Europe and the USA for AATD cases, which allow the recruitment of sufficient cases. Nevertheless, inspite of the lack of structured registries, large series of PAP cases have been assembled through single or closely connected clinical sites.[10,11] The Japanese PAP series, the largest available worldwide, has recently completed an open-label trial on GM-CSF aerosolization in autoimmune PAP patients. At our centre in Pavia, Italy we took advantage of the large series of PAP patients made available over 20 years from the institutional programme on WLL at the Fondazione IRCCS San Matteo Hospital. Using this series we initiated a randomized trial aimed at evaluating the superiority of WLL followed by inhaled GM-CSF over WLL alone. The study, currently in progress, includes the enrolment of 18 autoimmune PAP patients over a 36-month period.[12] To the best of our knowledge this is the first randomized trial designed to study PAP.

Conclusions

Registries are extremely powerful tools to improve our understanding of the natural history of rare disorders. In addition they are extremely useful for recruiting patients for clinical trials that otherwise could not be performed. Thus, a critical issue for neglected rare diseases is to create networks of reference centres with the aim of establishing national and international registries.

Conflict of interest statement

The authors of this manuscript have no conflict of interest to declare.

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